quiring hospitalization in the pharmacogenetic group, whereas three such events occurred in the control group. These trends, which are consistent across studies, suggest that uncommon but clinically meaningful outcomes should be considered in addition to intermediate end points (e.g., percentage of time in the therapeutic range) in a totality-of-evidence approach to assessing the usefulness of pharmacogenetic approaches.

The public's expectations for pharmacogenetics may arguably be declining. Logistic and evidentiary challenges have converged to create disillusionment regarding the relevance of pharmacogenetics. Many observers have called for randomized, controlled trials to address the translation lag. Methodologic rigor is critical in evidence assessment, and it is equally important to design experiments to definitively clarify issues of public health relevance. Randomization, in and of itself, does not accomplish this end. Rather, the choice of control, the treatment setting, characteristics of the population tested, the analytic approach, and end-point definition are likely to be the key considerations that determine the public health relevance of pharmacogenetic trials in the future. Future trials should use various methods to assess the clinical usefulness of pharmacogenetic interventions; these may include designs focused on assessing efficacy (emphasis on internal validity), effectiveness (emphasis on generalizability), and implementation effectiveness (emphasis on adoption and uptake).[2] These approaches are not mutually exclusive and, if combined, may expedite assessment of the effects of pharmacogenetic interventions on patients, providers, and health systems.[3,4]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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New Insights into the Dementia Epidemic

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Described in the early 1980s as "The Silent Epidemic," dementia in the elderly will soon become a clarion call for public health experts worldwide. The epidemic is largely explained by the prevalence of dementia in persons 80 years of age or older. In most countries around the world, especially wealthy ones, this "old old" population will continue to grow, and since it accounts for the largest proportion of dementia cases, the dementia epidemic will grow worldwide. The combined effects of longer lives and the dramatic bulge of baby boomers reaching old age will magnify the epidemic in future decades.

Although demographics will drive an increase in the number of dementia cases, recent reports — generally based on population-based community studies or survey data — point to declining age-specific prevalence or incidence rates among people born later in the first half of the 20th century (see table). We believe these reports are intriguing and inform our understanding of potentially modifiable factors that contribute to the epidemic of this common and often tragic condition. Knowing about contributing factors is especially important for the study and development of prevention strategies, and prevention is often the key to better control of epidemics, including epidemics of chronic diseases.

In 2005, Manton and colleagues published an intriguing article entitled "Declining Prevalence of Dementia in the U.S. Elderly Population."[1] On the basis of their analysis of 17 years of national long-term care surveys, conducted from 1982 through 1999, they reported a decrease in dementia prevalence from 5.7% to 2.9% during that period. They pointed to higher levels of education, a reduction in stroke rates, and other factors as possible contributors to the decrease.

This report was followed by an analysis of the U.S. Health and Retirement Study, an ongoing population-based, longitudinal survey of a nationally representative sample of adults 51 years of age or older.[2] In 1993, 12.2% of surveyed adults 70 years of age or older had cognitive impairment,

Selected Recent Studies of the Dementia Epidemic.

Study	Outcome	Data Source	Key Findings	Factors
Manton et al. (United States)[1]	Prevalence of severe cognitive impairment	National long-term care survey interviews, 1982–1999	Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)	Higher educational level, decline in stroke incidence
Langa et al. (United States)[2]	Prevalence of cognitive impairment	Ongoing population-based survey of people ≥51 yr of age	Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)	Higher educational level; combination of medical, lifestyle, demographic, and social factors
Schrijvers et al. (Rotterdam)[3]	Incidence of dementia	Population-based cohort ≥55 yr of age in 1990, extended in 2000	Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)	Higher educational level, reduction in vascular risk, decline in stroke incidence
Qiu et al. (Stockholm)[4]	Prevalence of DSM-III-R dementia*	Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004	Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence	Favorable changes in risk factors, especially vascular risk; healthier lifestyles
Matthews et al. (England)[5]†	Prevalence of dementia in 3 regions	Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)	Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)	Higher educational level, better prevention of vascular disease

* In the study by Qiu et al., dementia was diagnosed according to the criteria provided in the *Diagnostic and Statistical Manual of Mental Disorders,* third edition, revised (DSM-III-R).
† CFAS denotes Cognitive Function and Ageing Study.

as compared with 8.7% in 2002. Education was protective against cognitive impairment, and the results suggested that "overall, the combined impact of recent trends in medical, lifestyle, demographic, and social factors has been positive for the cognitive health of older Americans."[2]

Three recent studies of European populations support the optimistic view that dementia risk may be decreasing among older adults.[3-5] The Rotterdam Study,[3] in which researchers studied a cohort of inhabitants 55 years of age or older in 1990 and then studied a subcohort again in 2000, showed lower incidence rates in the 2000 subcohort; although the differences were not statistically significant, they were consistent across many groups. Statistical power was limited because the subcohort was smaller and had shorter follow-up than the overall cohort. Most intriguing was the observation of larger brain volumes and less extensive cerebral small-vessel disease on magnetic resonance imaging in persons born later. The authors compared scans of persons without dementia in 1995–1996 with scans obtained in 2005–2006 and reported that the differences supported their "finding of declining dementia incidence." They hypothesized that these changes were attributable to secular changes in education, population-level reductions in vascular risk factors, and an overall reduction in stroke incidence.

We also have recent reports from Sweden and England.[4,5] The Swedish study entailed two cross-sectional surveys of people 75 years of age or older who were living in central Stockholm in 1987–1989 and in 2001–2004, with analysis of death certificates to determine their survival status in December 1994 and June 2008, respectively. The age- and sex-standardized prevalence of dementia in the two surveys was similar: 17.5% in 1987–1989 and 17.9% in 2001–2004. However, because the hazard ratio for death was lower in the later cohort, including among persons with dementia, the authors argue that the incidence of dementia may have decreased during the period between surveys, probably owing to favorable changes in multiple risk and protective factors — notably, vascular risk factors and healthier lifestyles, especially among older people.

The most recent report compares the Cognitive Function and Ageing Study (CFAS) I and II,[5] two surveys of populations 65 years of age or older — CFAS I, conducted between 1989 and 1994, and CFAS II, conducted between 2008 and 2011, each with a sample size of more than 7500. The authors report standardized dementia prevalence rates of 8.3% in CFAS I, as compared with 6.5% in CFAS II. They conclude that populations born later have a lower risk of dementia than those born earlier, probably because of

higher education levels and better prevention of vascular disease, even in the face of countervailing factors such as diabetes and survival after stroke, which could increase age-specific dementia prevalence.

We study epidemics not just as an exercise in counting but especially to learn ways to reduce diseases' effects on individuals and populations. After early tentative, suggestive findings of decreasing rates over time, the consistency of these recent findings is encouraging and noteworthy, especially since the projected growth of the population older than 75 years guarantees a growing epidemic of dementia.

Eventually, we will have results of studies conducted over longer periods with presumably more definitive findings. But for now, the evidence supports the theory that better education and greater economic well-being enhance life expectancy and reduce the risk of late-life dementias in people who survive to old age. The results also suggest that controlling vascular and other risk factors during midlife and early old age has unexpected benefits. That is, individual risk-factor control may provide substantial public health benefits if it leads to lower rates of late-life dementias. Just as control of vascular risk factors has had measurable effects on public health through reduced rates of stroke and myocardial infarction, the recent English study concluded that estimates of national dementia prevalence based on CFAS I needed to be revised downward by 24% on the basis of the age- and sex-specific prevalence rates in 2011 found in CFAS II.[5]

An audio interview with Dr. Larson may be heard at NEJM.org

Recent attention and resources have been directed at identifying preclinical dementia, especially Alzheimer's disease, and at preventive-drug trials that enroll the very few persons who are at extremely high risk for the disease, such as those with dominantly inherited mutations (which account for <1% of cases). Although this strategy is important for the development of effective treatments, the recent studies highlighted above illustrate the potential for deriving widespread public health benefits from such lifestyle interventions as improving educational opportunities in both early and later life, reducing vascular risk factors, and promoting greater physical activity. These studies also remind us that dementia is a syndrome — a complex of symptoms with multiple causes — making it similar to most late-life chronic diseases. In fact, population-based studies have convincingly demonstrated that the vast majority of dementia cases, especially those occurring very late in life, tend to involve a mixture of Alzheimer's disease, vascular disease, and other degenerative factors.

Research on preventing late-life dementias should explore ways of reducing risk factors at both the societal and the personal levels. We don't know the extent to which better risk-factor control can reduce dementia rates. However, a potentially ominous trend that could lead to a reversal of the decrease in risk is the growing prevalence of obesity and diabetes among middle-aged and younger people. Other factors to consider in the United States and other countries with increasingly racially and ethnically diverse older populations are changes seen in some groups of second- and third-generation Americans that might drive increased risk for vascular disease. Improvement in life expectancy will certainly lead to a net increase in the number of older people who have dementia late in their lives. This fact alone, plus population trends, justifies the value of learning more about lifestyle and risk factors that affect dementia rates. Given recent reports of trends in dementia incidence and prevalence, we believe that research to uncover influences on these trends has great promise.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government.

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